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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF ANDREAS WERNER  
SUPERSAXO ET AL

Group Art Unit: 1619

SERIAL NO.: 09/306,006

Examiner: S. SHARAREH

FILED: JUNE 5, 1999

FOR: USE OF NANODISPERSIONS IN PHARMA-  
CEUTICAL END FORMULATIONS

Commissioner for Patents

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DECLARATION UNDER RULE 132

I, Andreas Werner Supersaxo, a citizen of the Swiss Confederation, residing in Baar, Switzerland, hereby declare:

1. That I am a co-inventor of the invention disclosed and claimed in the above identified patent application;
2. That I have been employed by Vesifact AG since January 1, 1998, specializing in research of nano-sized carrier systems for life science products;
3. That I am presently head of R & D, and have held this position since January 1, 1998;
4. That I am engaged in the research and development of nano-sized carrier systems for life science products;
5. That I consider myself an Expert in preparation of drug delivery systems, especially lipid based delivery systems such as liposomes, mixed micelles and microemulsions;
6. That prior to my employment at Vesifact AG, I was an employee of F. Hoffmann-La Roche AG Basel, Switzerland and of Syntex Research, Palo Alto, California, USA;
7. That I received my Ph. D. in pharmaceutics in 1986 at the Swiss Federal Institute of Technology, Department of Physical Pharmacy, Zurich, Switzerland;
8. That I am a named inventor in U.S. Patents Nos.: 5,376,646; 5,470,582; 5,759,827 and 6,030,602, and
9. That I carried out the following preparative Examples (1) – (7).

The following tests show that the use of the polyethoxylated coemulsifier as claimed in the present invention leads to nanodispersions wherein the particle size is smaller than in the nanodispersion wherein polyethoxylated sorbitan fatty acid ester is used. This is a surprising effect.

Secondly, tests have been made with non-ethoxylated coemulsifiers with a similar HLB-value. The particle sizes of these "nanodisperisons" are much larger than those of the nanodispersions according to the present invention.

Table 1.

Nano-dispersion	Coemulsifier (INCI name)	Coemulsifier (chemical name)	HLB	Appearance	Particle size <sup>1)</sup> [nm]
1*	TWEEN 80 (Polysorbate 80)	polyethoxylated sorbitan fatty acid ester	15	opalescent, transparent	22.3
2**	SOLUTOL HS 15 (PEG-15 Hydroxystearate)	polyethoxylated fatty acid	14-16	opalescent, transparent	12.8
3**	SIMUSOL 98 (Oleth-20)	polyethoxylated fatty alcohol	15.3	opalescent, transparent	14.2
4**	AQUALOSE W20 (Laneth-20)	polyethoxylated lanolin	16	opalescent, transparent	15.0
5**	CREMOPHOR EL (PEG-35 Castor Oil)	polyethoxylated triglyceride	12-14	opalescent, transparent	12.0
6	SUCRO ESTER WE 15 (Saccharose Monopalmitate)	Sugar fatty acid ester (non- polyethoxylated)	15	milky	> 2000
7	RYOTO POLYGLY ESTER O-15D (Decaglycerol Oleate)	Polyglycerine fatty acid ester (non- polyethoxylated)	15	milky	241

\* = Example 2 of WO 96/37192

\*\* = according to the invention

- 1) The particle size of the nanodispersions were determined by dynamic light scattering (apparatus: Nicomp 380 Submicron Particle Sizer; evaluation by volume weighted Gaussian Analysis).

List of the composition of the nanodispersions 1 – 7

All nanodispersions have been prepared according to WO 96/37192.

Nanodispersion 1 (Prior Art; Example 2 of WO 96/37192)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
TWEEN 80 (HLB: 15)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 2 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
SOLUTOL HS 15 (HLB: 14-16)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 3 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
SIMUSOL 98 (HLB: 15.3)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 4 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
AQUALOSE W20 (HLB: 16)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 5 (Invention)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
CREMOPHOR EL (HLB: 12-14)	3.35
10 mM Phosphate buffer pH 6.0	90.00

Nanodispersion 6 (Comparative Example)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
SUCRO ESTER WE 15 (HLB: 15)	3.35
10 mM Phosphate buffer pH 6.0	90.00

## Nanodispersion 7 (Comparative Example)

Ingredients	Concentration [%]
Ceramide 3B	0.15
LIPOID S100	1.70
Ethanol (abs.)	1.40
MIGLYOL 812	3.40
RYOTO POLYGLY ESTER 0-15D (HLB: 15)	3.35
10 mM Phosphate buffer pH 6.0	90.00

It can be seen from Table 1 that the use of the coemulsifier of the present invention leads to nanodispersions (nanodispersions 2 - 5) with a smaller particle size than

- (i) the nanodispersion of the prior art (nanodispersion 1) and
- (ii) the comparative "nanodispersions", wherein non-ethoxylated coemulsifiers with similar HLB-values are used (nanodispersions 6 and 7).

I declare that such improvements could not have been expected by a person skilled in the art.

I, Andreas Werner Supersaxo, further declare that all statements made herein of personal knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 18<sup>th</sup> day of May, 2004

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Andreas Werner Supersaxo